Remarks/Arguments

Claims and 15-24 are pending. In response to the Examiner's comments, claim 9 is amended to insert "a" in front of "mouse". In response to the rejection under § 112, claims 9 and 17 are amendment to recite that the targeting vector comprises homology arms directing the targeting vector to a specific chromosomal location. Support for this amendment is found in the specification at paragraph 14. No new matter is added by these amendments. These amendments are believed to place the claims in condition for allowance and/or in better form for consideration on appeal and the Examiner is respectfully requested to enter the above amendments.

I. Rejections under 35 USC §112, first paragraph

Claims 17-20 were rejected for lack of enablement on the basis that the claims encompass targeting any specific chromosomal location within a genome using the ubiquitin promoter. The Examiner states that

"the specification has failed to teach how one of skill in the art can target a specific chromosomal location with the claimed method of using a targeting vector comprising a ubiquitin promoter. As discussed above the ubiquitin promoter is ubiquitous, and would express in all eukaryotic cells. The specification teaches that certain genes are targeted, but the specification fails to teach that a specific chromosomal location was targeted. The working examples in the instant specification as well as the entire specification fail to teach how one of skill in the art would target a specific chromosomal location using the claimed method."

In response, claim 17 is amended to recite that the vector comprises homology arms which direct the targeting vector to a specific chromosomal location. Applicants respectfully submit that one of skill in the art knows that to direct a targeting vector to a specific chromosomal location, the homology between the homology arms and the corresponding endogenous sequence is accomplished via homologous recombination (paragraph 14, page 2-3 and Example 1, paragraph 41). Applicants attach a copy of co-owned U.S. 6,586,251, which describes the use of targeting vectors with homologous arms which direct the targeting vector to a specific chromosomal location within the genome by virtue of the homology that exists between the homology arms and the corresponding endogenous sequence and introduce the targeting vector by homologous recombination. Accordingly, in light of the above amendments and remarks, it is believed this rejection may now be withdrawn.

II. Rejections under 35 USC §103(a)

Claims 9 and 15-24 were rejected as being unpatentable over Rohozinski et al. (Genesis

2002 32:1-7), in view of Tsirigotis et al. (BioTechniques 2001 31:120-130) and Ghazizadeh *et al.* (1998) J. of Investigative Dermatology, 111:492-496.

The invention as claimed. The amended claims are drawn to *in vitro* methods of targeting a mouse embryonic stem (ES) cell through the introduction of a targeting vector comprising a ubiquitin promoter and homology arms directing the targeting vector to a specific chromosomal location, and to methods of targeting a targeting vector into mouse ES cells through the introduction of a targeting vector comprising a ubiquitin promoter and homology arms directing the targeting vector to a specific chromosomal location.

Rohozinski et al.. Rohozinski et al. describe gene targeting via homologous recombination which targeted 2 genes on the Y chromosome.

Tsirigotis et al.. Tsirigotis et al. describes construct comprising a human ubiquitin C promoter and a GFP reporter gene.

The Ghazizadeh *et al.* reference. Ghazizadeh *et al.* describe using a retrovirus vector comprising the lacZ gene and the neomycin phophotransferase gene to select non-transformed porcine keratinocytes using G418 to select cells which are not expressing neomycin phophotransferase.

The analysis under §103(a). Applicants respectfully submit that the obviousness rejection should be withdrawn for the following reasons:

1. Nothing in the combined prior art references suggests the combination of a targeting vector and a ubiquitin promoter; moreover, nothing in the prior art suggests a method of improving targeting efficiency.

The prior art does not suggest the use a the ubiquiting promoter in the context of a targeting vector. Rohozinski et al. shows that gene targeting is known. Tsirigotis et al. use a construct having a ubiquitin promoter for non-targeted random integration. Ghazizadeh et al. neither disclose a targeting vector or the use of the ubiquitin promoter, let alone their combination.

As the above analysis shows, even combining the cited prior art references fails to disclose a method for targeting mouse ES cells with a targeting vector comprising a ubiquitin promoter and two homology arms. Importantly, nothing in the combined references teaches or suggests a method for improving targeting efficiency.

2. The unexpected advantages of the instant method overcome a *prima facie* case of obviousness.

It is respectfully submitted that even if for the sake of argument one assumes that the

Examiner has established a *prima facie* case of obviousness with the combined cited art, such a case is overcome by the unexpected advantages of the instant invention. The Examiner's attention is directed to Table 2 at page 11 of the specification. Applicants show that the use of a targeting vector having a ubiquitin promoter and two homology arms not only resulted in an average 6-fold increase in the number of surviving colonies generated (col. 7 of Table 2), but the instant method results in a 4-fold increase in the targeting efficiency (col. 8). This means that the instant method allows one to target a gene into a specific chromosomal location more efficiently than by prior art methods, vastly reducing the labor involved in generating cells with specifically desired modifications. Accordingly, in light of the above amendments and remarks and the showing of unexpected advantages of the instant invention, it is respectfully requested that this rejection be withdrawn.

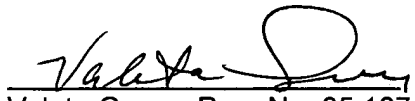
Conclusion

It is believed that this document is fully responsive to the Office action dated 2 March 2006. In light of the above amendments and remarks, it is believed that the claims are now in condition for allowance, and such action is respectfully urged.

Fees

Although it is believed that no fees are due, in the event the Patent Office determines that fees are due, the Commissioner is hereby authorized to charge Deposit Account Number 18-0650 in the amount of any fees deemed to be due.

Respectfully submittted,



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